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HOW TO IDENTIFY CORONARY ARTERY DISEASE IN AN ASYMPTOMATIC HYPERTENSIVE PATIENT?

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Hypertension and coronary artery disease: current status

Coronary artery disease (CAD) constitutes the leading cause of death and is a major cause of morbidity and impaired quality of life worldwide; hypertensives compared to normotensives exhibit a 2- to 3-fold higher prevalence of CAD [1–4]. oreover, 60% of patients who suffer from CAD have hypertension, suggesting a close association between hypertensive disease and the pathophysiology of CAD [1–5].

The clinical need to identify asymptomatic CAD

CAD has a long asymptomatic latent period. Many subjects, even those with an advanced form of the disease, do not show symptoms before experiencing a major event such as sudden cardiac death, unstable angina, myocardial infarction, or congestive heart failure [3, 6, 7]. Additionally, there is in clinical practice the common need to exclude CAD in asymptomatic hypertensives who undergo preoperative risk assessment, who present with new-onset atrial fibrillation, or who are on clinical work-up after episodes of ventricular tachycardia or syncope [6, 7]. Based on the above, the aim of this newsletter is to provide an approach to risk assessment of CAD in asymptomatic hypertensive patients.

Pathophysiology of myocardial ischaemia in hypertension

In hypertensive patients, myocardial ischaemia is caused by anatomical and pathophysiological factors different to those of 'classic' CAD [3, 8]. Apart from the atherosclerotic obstruction of the large epicardial coronary arteries, reduced vasodilator capacity of the coronary microcirculation, caused mainly by arteriolar hypertrophy and endothelial dysfunction, is very often present [3, 8–11]. Furthermore, coronary flow reserve is reduced in hypertensives due to several pathophysiological mechanisms such as increased haemodynamic load, left ventricular (LV) mass and end-systolic stress, inadequate angiogenesis, extravascular compression, reduction in the overall maximal cross-sectional area of the microcirculatory bed along with subclinical inflammation, endothelial dysfunction, and activation of the sympathetic nervous system and the renin angiotensin system [3, 8–11]. From a clinical point of view, reduced coronary flow reserve could lead, at least during the period of stress, to reduced subendocardial coronary perfusion and ischaemia, and impaired diastolic and systolic functions [3, 8–11]. Additionally, adverse alterations of the thrombosis/fibrinolysis system and haematic viscosity contribute to a prothrombotic state and CAD clinical events [8].

All the above-mentioned mechanisms lead to an imbalance of myocardial oxygen demand and supply in hypertension, and contribute to either the clinical expression of ischaemic events or to silent ischaemia [12–14]. The latter is very common in patients without adequate blood pressure (BP) control as well as in elderly untreated hypertensives, suggestive of a pronounced ischaemic burden [12–14]. However, the data on the prognostic significance of silent ischaemia is sparse and contradictory. In the Baltimore Longitudinal Aging Study, there was no association of transient ischaemia with cardiac end-points [13], but in a Swedish study of men born in 1914, the presence of silent ischaemia constituted a strong predictor of cardiac events [14]. Nowadays, if clinical data on transient silent ischaemia is available, it should only be used cautiously in terms of assessing the global ischaemic myocardial burden.

Assessment of CAD risk in hypertension: combining risk scores and target organ damage

In the setting of asymptomatic hypertensive individuals, a diagnosis of CAD should be guided by total cardiovascular risk [4–7]. According to the ESH guidelines [4, 5], high risk hypertensives are defined as those with systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg, diabetes (types 1 and 2), a severely elevated single risk factor or more than three cardiovascular risk factors, a history of previous cardiovascular or renal disease and the presence of target organ damage (such as microalbuminuria or proteinuria, an estimated glomerular filtration rate by the Cockroft-Gault or MDRD formulae of less than 60 ml/min/1.73 m^2, concentric left ventricular hypertrophy, carotid wall thickening with intima media thickness over 0.9 mm or the presence of plaque, carotid-femoral pulse wave velocity over 12 m/sec and ankle/brachial BP index less than 0.9). Such patients should undergo further diagnostic testing for the presence of CAD even if they are currently asymptomatic. In most remaining hypertensive patients, the use of established risk scores based on the Framingham study, the SCORE project and the HeartScore constitute the means for classification into low, average, high and very high risk by taking also into consideration the levels of BP [4–8].

Although the physical risks of exercise testing are negligible, false-positive test results may result in inappropriate further testing and patients' anxiety, along with either work or insurance problems. Thus, if a hypertensive asymptomatic individual is considered low-risk after careful assessment, no further investigation of CAD is needed. If, however, the asymptomatic hypertensive is stratified as average or high/very high risk, a functional stress-test is recommended.

Tests for CAD risk assessment in the asymptomatic hypertensive patient

Evaluation of target organ damage

Heart

Electrocardiogram

According to the latest ESH guidelines, a resting ECG is reasonable for cardiovascular risk assessment in asymptomatic individuals with hypertension [4, 5]. Epidemiological data has shown that a 12-lead ECG is predictive of events in asymptomatic adults, and that specific findings such as left ventricular hypertrophy (LVH), QRS prolongation, ST-segment depression, T-wave inversion and Q waves are indicative of the augmented likelihood of adverse cardiovascular events along with the presence of arrhythmias [7, 15]. Most importantly, ECG reclassifies risk compared to standard assessment in the Women's Health Initiative and in the Cleveland Clinic study [7].

Resting cardiac echocardiography

In asymptomatic hypertensive patients, echocardiography is essential for CAD risk assessment and detection of LVH [4, 5]. For a hypertensive individual, the MAVI study found that each 39 g/m^2 greater LV mass index was accompanied by a 40% higher risk of cardiovascular events. In a Greek study with a 6-years follow-up, the presence of LVH was associated with a 1.52 hazard ratio of cardiovascular events [4, 5, 16]. Apart from the LVH, those with either concentric remodelling or LVH had a 2-fold higher cardiovascular risk [4, 5]. Additionally, both ejection fraction and LV fractional shortening predicted events as well as LV diastolic function (transmitral blood flow or tissue Doppler imaging). Segmental defects of LV wall contraction may be due to prior silent infarction or ischaemia and should be further investigated [4, 5, 7].

Blood vessels

Carotid intima-media thickness

Carotid intima-media thickness evaluation predicts the incidence of cardiac events. More specifically, the ARIC study found that for every 0.19-mm increment of intima-media thickness, the risk of death of myocardial infarction was augmented by 36% [4, 5, 7]. Notably, the link between carotid intima-media thickness and events is linear and continuous and the use of the cut-off point value of > 0.9 mm is a conservative estimate.

Ankle-brachial index

This office-based test for peripheral arterial disease provides prognostic information regarding CAD, especially in patients at intermediate risk. A value of < 0.9 signifies the presence of peripheral arterial disease with a stenosis > 50% and is a predictor of adverse cardiac events [4, 5, 7].

Arterial stiffness

Carotid-to-femoral pulse wave velocity is an independent predictor of coronary events in hypertension. Although the relationship of stiffness to events is continuous, the cut-off point of > 12 m/sec is commonly used [4, 5].

Kidney

Glomerular filtration rate

Renal dysfunction assessed by estimated glomerular filtration rate (eGFR), using either the abbreviated MDRD formula or the Cockcroft-Gault formula, is related to adverse outcome [4, 5, 16]. In a hypertensive population, eGFR between 15–59 ml/min/1.73 m^2 augmented by 66% the risk for events, even after adjustment for LVH and baseline confounders [16]. In the ADVANCE trial, a 50% decrease in eGFR increased by 2.2-fold the risk of cardiovascular events and, in concordance with the VALUE trial, underscored the predictive value of eGFR [4, 5, 17].

Microalbuminuria

In hypertension microalbuminuria, even below the established threshold values (albumin to creatinine ratio < 30 mg/g), has a cardiovascular predictive value and there is a continuous relationship of CAD risk with levels as low as ≥ 3.9 mg/g in men and 7.5 mg/g in women [4, 5]. This may be due to the fact that albuminuria reflects generalised vascular dysfunction and is a unique integrator of endothelial irregularities, inflammatory activation and atherosclerosis progression [18].

Functional testing for CAD

Exercise electrocardiography

Exercise ECG is indicated in hypertensives with average and high risk for assessment of asymptomatic CAD [7, 8]. In hypertension, diastolic dysfunction, LV hypertrophy, increased wall stress and subendocardial ischaemia commonly decrease the specificity and sensitivity of exercise testing [3, 8]. Meta-analysis has shown that this test has mean sensitivity and specificity of 68% and 77% respectively, while other works have shown specificity as high as 90% [3, 8, 19]. Exercise tolerance is decreased in patients with poor BP control, and severe systemic hypertension may cause exercise-induced ST depression in the absence of atherosclerosis, reducing diagnostic accuracy [3, 8]. Furthermore, hypertensives with bundle branch block, atrial fibrillation and signs of left ventricular hypertrophy or ischaemic disease in resting ECG, along with orthopaedic problems that would preclude maximal effort on the bicycle or treadmill, should be excluded from exercise testing [20]. However, despite the relatively low sensitivity, an exercise test has an excellent negative predictive value and is ideal for the initial screening of average and high risk hypertensives.

Myocardial perfusion imaging

Stress myocardial perfusion imaging may be considered in high-risk hypertensive patients, especially if they are diabetic [7]. In 3,664 asymptomatic high-risk patients re-

ferred for stress myocardial perfusion imaging, those with > 7.5% myocardial ischaemia had an annual event rate of 3.2% [21]. The accuracy of perfusion is high (sensitivity of 85–90% and specificity of 70%), and comparable to stress-echocardiography in hypertensive patients, and there are reports of higher sensitivity of myocardial perfusion imaging compared to stress-echocardiography [8, 22, 23]. However, because of the time, cost and radiation exposure, a nuclear test might no longer be competitive especially in the setting of asymptomatic hypertension [7].

Stress-echocardiography

Stress-echocardiography is not indicated in asymptomatic low-risk adults or in average-risk ones unless the exercise ECG test performed in the latter group is positive, ambiguous, non-diagnostic, submaximal or inconclusive [3, 7]. Stress echocardiography can be performed with dynamic forms of exercise, including treadmill and bicycle, as well as with pharmacologic stress, most often using dobutamine and dipyridamole [24]. The diagnostic performance of the test is highly dependent on the expertise of the physician, and acquisition as well as interpretation, of the images [24].

A poor acoustic window makes any modality of stress echocardiography unfeasible to perform, and specific contraindications to dipyridamole (or adenosine) echocardiography include the presence of severe conduction disturbances and bronchopneumopathic disease. Additionally, dobutamine causes an increase in systolic BP in the majority of patients and should be used judiciously in hypertension [24].

Cumulative evidence suggests that in hypertension stress-echocardiography has excellent predictive value [22, 23, 25] and that among stressors, dobutamine may yield better diagnostic accuracy compared to dipyridamole [3, 8, 22, 23]. Furthermore, in patients with exercise-induced ST segment depression, stress-echocardiography has a higher specificity to myocardial perfusion scintigraphy [3, 23], whereas in patients with LVH and right bundle branch block, dipyridamole shows increased diagnostic accuracy [22, 23]. The low sensitivity of dipyridamole stress-echocardiography in single-vessel disease can be resolved with the atropine protocol [8].

Patients with a negative stress-echocardiography test are expected to have either normal coronary arteries or anatomically minor and prognostically benign forms of CAD; thus coronary angiography can be safely avoided.

Computed tomography for coronary calcium

Evaluation of coronary calcium could be considered in asymptomatic hypertensives with average and high risk in men older than 40 years and women older than 50 years [7]. Average-risk patients with an elevated coronary calcium score > 300 have a 2.8% annual rate of cardiac death or myocardial infarction [7]. However, due to the issue of radiation and in the present era of cost-effectiveness, this modality cannot be encouraged in the setting of asymptomatic hypertensives.

Proposed algorithm for identification of CAD in asymptomatic hypertensives: a three-step approach (Figure 1)

First step: risk classification

In order to better evaluate an asymptomatic hypertensive patient for the presence of significant CAD, a thorough history and clinical examination is needed. Moreover, an ECG is performed, as well as resting echocardiographic examination, in parallel with a search for target organ damage according to current guidelines [4, 5]. Based on all the above, the patient is classified as low, average or high/very high risk.

Second step: functional testing for CAD

In low-risk individuals, no further testing is considered. For patients in the average and high-risk groups, an exercise ECG test is done if applicable according to the established criteria [20]. In other patients, stress-echocardiography or myocardial perfusion imaging modalities are considered the initial step. Based on negativity for ischaemia of the functional stress-test, the patient is advised to continue current treatment. However,an asymptomatic hypertensive patient with a positive stress-test should be referred for coronary angiography.

Third step: coronary angiography

In the small fraction of patients referred for coronary angiography, if significant epicardial CAD is found, ischaemia-driven revascularisation in order to improve the prognosis should be implemented.

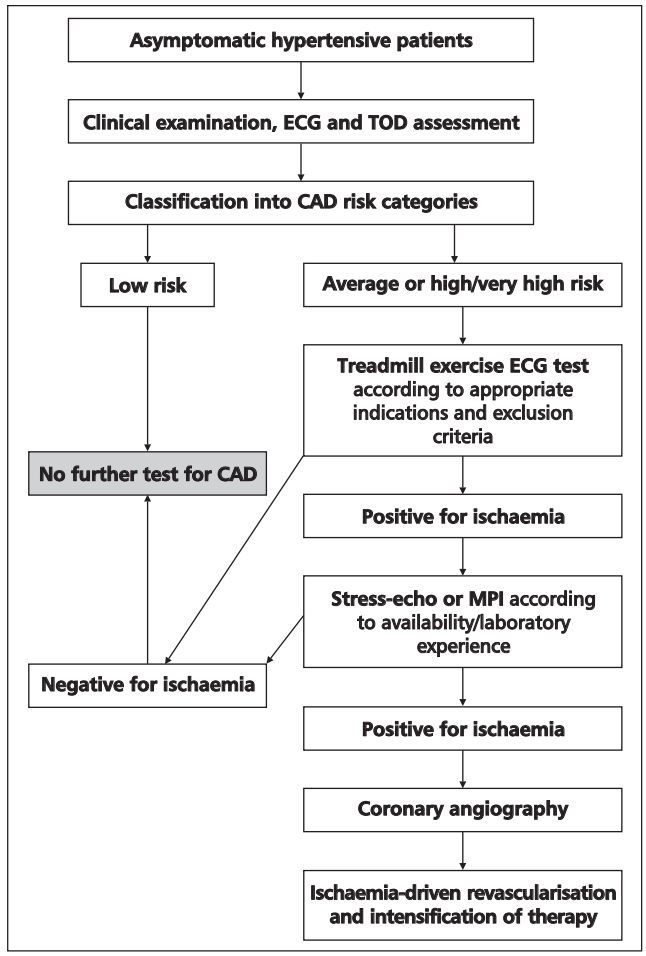

Figure 1. Simplified diagnostic algorithm for identifying CAD in asymptomatic hypertensive patients

Summary

The purpose of screening for possible CAD in asymptomatic hypertensive patients is to prolong life and improve its quality because of early detection. Furthermore, assessment of risk for asymptomatic CAD in hypertension aids clinicians in making evidence-based decisions on the intensity of lifestyle and pharmacological interventions, in order to reduce adverse events and optimise cardiovascular care. From another point of view, if a certain hypertensive individual based on estimated risk is considered of low probability for significant CAD, no unjustified testing is performed, in order to spare resources. Nevertheless, a reduction of risk factors should be attempted in all hypertensives, while identification of functional impairment by stress-tests may further improve patients' compliance. Finally, in the rare cases of obstructive epicardial CAD in asymptomatic hypertensives, ischaemia-driven revascularisation can ameliorate the long-term cardiac outcome.

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